Remarks

Claim Status - Election/Restriction

Claims 1-5, 12, 16, 43, 48-50, and 72-95 were previously pending. Claims 1, 3, 4, 5, 12, 16, 43, 72-76, 78-86, and 88-95 are currently amended. Claims 48-50 are canceled herewith. Claims 6-11, 13-15, 17-42, 44-47, 51-71, and 96-102 have been withdrawn. New dependent claims 103-109 are added herewith. No new matter is introduced.

A discrepancy in the claim pendency currently exists in the record. Applicants respectfully request that the Examiner clarify on the record the status of the claims. In the Office Action mailed from the USPTO on January 23, 2003 point number 4 indicated that claim 43 was withdrawn from consideration because it belongs to the invention of group II. The invention of Group II is a "soluble extract that mediates RNA interference". In the Office Action Summary, page 1 of the Office Action mailed from the USPTO on March 16, 2004, claim 43 is referred to as pending and claim 42 is indicated to be withdrawn from consideration. On page 2 of the same Office Action both claims 42 and 43 are indicated to be pending. In the present response to Office Action Applicants have treated claim 42 as being withdrawn and claim 43 as pending. It is Applicants' understanding that claim 43 is pending because it relates to a pharmaceutical composition of an isolated RNA rather than a soluble extract.

Additionally, the summary of the Office Action mailed from the USPTO on March 16, 2004, and the description on page 2 of the same Office Action indicate that claims 96 and 102 are withdrawn. The status of independent claim 100 and dependent claims 97-99 and 101 is not listed. Applicants have treated all of claims 96-102 as being withdrawn in view of the status of claims 96 and 102.

Accordingly, claims 1-5, 12, 16, 43, 72-95, and 103-109 are pending, of which claims 1, 5, 12, 16, 43, 72-76, 80-86, and 90-95 are independent claims.

Support for the claim amendments is found throughout the specification and original claims. In particular support for the limitation "has sequence correspondence to an mRNA" is found in the specification at least on page 2 lines 23-26 and page 3 lines 17-19.

Support for the limitation that "mediates RNA interference by directing cleavage of the mRNA" is found in the specification at least on page 3 lines 13-17 and page 4 lines 20-25.

Support for the limitation that the RNA includes one or more nucleotides with "a non-naturally occurring nucleotide or deoxyribonucleotide" is found in the specification at least on page 3 lines 6-8.

Support for the amendment of claim 12 to add the limitations of withdrawn claim 9 are found in original claim 9. Support for the amendment of claim 16 to add the limitations of withdrawn claim 15 are found in original claim 15.

Support for new claims 103-105 is found in original claims 3, 78, and 88, all of which included the limitation that the isolated RNA is an analog of a naturally occurring RNA.

Support for new claims 106-107, which add the limitation that the isolated RNA is complementary to the mRNA or gene is found in the specification at least in Example 2 on page 36 lines 15-19, describing data as well as in the paragraph spanning pages 2 and 3, which describes the process of RNAi and indicates that it is not necessary for perfect correspondence, implying that perfect correspondence is one embodiment.

Support for new claim 108 is found in the specification at least on page 4, lines 20-21, page 16 lines 3-6 and page 17, lines 18-21.

Support for new claim 109 is found in the specification at least on page 4, lines 20-21, page 14 lines 9-11, and page 60 lines 11-15.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 1-5, 12, 16, 48-50, and 72-75 and has rejected the new claims 76-95 under 35 U.S.C. § 112, first paragraph, for allegedly failing to satisfy the written description requirement. The Examiner alleges that the written description requirement is not satisfied because the structural limitation i.e. "...the specific binding site sequence or the specified sequence location of RNA of a length from about 21 to about 23 nucleotides, where the biological function is situated that promotes the RNA interference is not described." (Office Action page 2, # 5 and page 4 first full paragraph.)

In response, Applicants have amended the claims to clarify that the isolated RNA has sequence correspondence with an mRNA. This limitation adequately describes the binding specificity of the RNA. The present claims 1-5, 43, 76-81, 86-91, and 103-109 are drawn to a

genus of nucleic acids that share the following common structural features: (i) they are isolated RNAs, (ii) they have the length of about 21-23 nucleotides, (iii) they have a sequence that corresponds to (claims 1-5, 43, 76-81, 86-91, 103-106 and 108-109), or is complementary to (new dependent claims 107-108), a target RNA or gene and they are able to induce degradation of the target RNA by the mechanism of RNA interference (RNAi) or transcriptional silencing of the gene. Claims 72-75,82-85, and 92-95 relate to isolated DNA that encodes RNA having these same properties. Applicants have therefore included sufficient structural data to define the genus of nucleic acids of the invention.

An important aspect of the present invention lies in the knowledge that the structural requirement of size and complementarity are sufficient for a person of ordinary skill in the art to practice the invention. The commercial and scientific success of this discovery lies in its seemingly simplistic elegance. The testament to this is an entire discipline in the academic scientific community that has practiced the invention to reproduce the teachings of the invention. The leading scientific journals Nature, Cell and Science include many research articles that show how the teachings of the instant patent application have been utilized by those of ordinary skill in the art to practice the invention. In addition a thriving sector of the biological industry has developed due to the RNAi technologies, the key features of which are described by Applicants in this patent application and the present claims.

In addition, the Examiner argues that since "the instant claims do not recite structural limitation (sequence identity or SEQ ID Nos.) and the specification is not (sic) be read into the claims...the instant claims do not meet written description guidelines." (Office Action page 3 first full paragraph). SEQ ID Nos. are not an essential limitation of the invention and are thus, not required for the patentability of the claims. The invention is based, at least in part, on the recognition that RNA having certain critical structural features, such as a size of about 21 to about 23 nucleotides in length and sequence correspondence (or complementarity) with a target mRNA was sufficient to induce degradation of the target mRNA by RNAi or to inactivate a corresponding gene by transcriptional silencing when exposed to the target mRNA/gene in a cellular system. These structural and functional properties are associated with the entire genus of claimed molecules. The genus of molecules is broad but adequately described. The invention

would not be adequately captured in the claims if specific nucleotides or SEQ ID NOs. were included in the claims.

The Examiner has indicated that Applicants' arguments with respect to support in the specification for the claims is not sufficient to overcome the rejection because limitations from the specification are not read into the claims. Applicants previously pointed to pages in the specification to identify the portions of the specification that demonstrate applicants possession of the invention at the time of filing. At the time that the application was filed Applicants fully described each of the structural and functional characteristics listed above and presently included in the pending claims. That description is adequate to support the pending claims. Applicants are not attempting to read limitations from the specification into the claims.

The language used in the claims of the present application is consistent with similar claims that have been issued in U.S. patents. For example, the Fire *et al.* (US Patent No. 6,506,559) and Baulcombe *et al.* (US Patent No. 6,531,647) patents cited in the Office Action have issued claims drawn to methods of using large genera of nucleic acids, even broader than the present claims. Neither of these genera of nucleic acids is limited by the use of SEQ ID Nos. to describe the structure of the members of the genera.

Additionally, when the facts under consideration herein are applied in the context of case law and the written description guidelines, it is clear that Applicants have provided an adequate written description for the claimed invention. A relevant inquiry in analyzing written description is whether the application "clearly allow persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed"[1] or, in other words, that the inventor was in "possession" of the invention.[2] The instant invention, as discussed above, is based on the finding that isolated RNA possessing certain structural properties (which are set forth in the claims) have the ability to interfere with target mRNA processing by having a complementary sequence that interacts with and causes cleavage of the target mRNA. This invention is adequately and completely described throughout the specification. The structural and functional properties of the claimed RNA are incorporated into the pending claims and fully described in the specification. It is clear that Applicants had possession of the complete claimed invention at the

[1] *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).
[2] *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996).

time that the application was filed and an adequate written description of the claimed invention was included in the specification.

The Examiner's arguments for a lack of written description seems to be based, at least in part, on the principal that a claim to a DNA sequence must be described in terms of a sequence of nucleotides. For example, the Examiner relies on *Fiers* (paragraph bridging pages 4 and 5). The issue in *Fiers* was whether there was support for a DNA encoding b-IF where the only structural characteristic capable of identifying the DNA was its sequence. The claimed RNA and DNA molecules have common structural features and do not need to be defined by sequence. Additionally each of 1-5, 12, 16, 43, 76-81, 86-91, and 103-109 are directed to RNA, not DNA sequences.

The Examiner has objected to the scope of the analogs and has indicated that the claims include "millions of thousands of variant fragment by permutations and combination (by the language- deletion, substitution, addition or alteration of one or more nucleotides)." (Office Action page 4 first full paragraph) Applicants have deleted the term "RNA analogs" from pending claims 3, 78, and 88 and introduced new independent claims 103-105, directed to analogs. To expedite prosecution Applicants have also added the limitation to claims 4, 79, and 89 that the analog differs from the isolated RNA by the addition, deletion, substitution or alteration of one or more nucleotides "wherein the one or more nucleotides is a non-naturally occurring nucleotide or deoxyribonucleotide." The language serves to clarify that the analog is based on the use of one or more non-naturally occurring nucleotides, as set forth in the specification. Non-naturally occurring nucleotides are well-known in the art and are routinely used in DNA and RNA based methods.

Accordingly Applicants request that the Examiner withdraw the claim rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections Under 35 U.S.C. § 102

A. Claims 76-95 have been rejected as being anticipated by the Fire et al patent (US 6,506,559). Applicants disagree. Fire et al teach nucleic acids of length of at least 25 nucleotides that mediate RNAi. In contrast, the present claims are limited to nucleic acids that are about 21-23 nucleotides in length. Therefore, the nucleic acid molecules described by Fire et

al do not anticipate the claimed nucleic acids. Accordingly, Applicants respectfully request that the Examiner withdraw the claim rejection under 35 U.S.C. § 102.

B. Claims 1, 3-5, 12, 16, 42, 48-50, 76, 78-86, and 88-95 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Baulcombe *et al.* (US 6,531,647). Baulcombe et al describe a class of nucleic acid molecules that are referred to as fiRNA. The fiRNA nucleic acids of the Baulcombe et al patent "...may be 300 nucleotides in length, possibly about 200 nucleotides, or about 100 nucleotides. It may be possible to use oligonucleotides of much shorter length, 14-23 nucleotides. Longer fragments, and generally even longer than 300 nucleotides are preferable where possible if the fiRNA is produced by transcription or if the short fragments are not protected from cytoplasmic nuclease activity." (Column 7, lines 38-44). Additionally, the Baulcombe invention is carried out in plants and described to be applicable only in plants.

The Baulcombe et al patent does not anticipate the claimed invention because it does not teach each element of the claims. Baulcombe et al disclose a large genus of nucleic acids ranging from 14 to 300 nucleotides in length that mediate the silencing of a target nucleotide sequence. In contrast each of pending claims 1-3, 12, 16, 43, 76-79, 81, 86-88, and 91 includes the limitation that the isolated RNA has about 21 to 23 nucleotides in length. The nucleic acids of the claimed invention represent a distinct species from the genus of nucleic acid described in the Baulcombe et al patent, and are, thus, not anticipated by the disclosure of Baulcombe et al. Furthermore, as shown by the paragraph from the Baulcombe et al patent cited above, Baulcombe et al teach that the nucleic acid of "...longer fragments, and generally even longer than 300 nucleotides are preferred for activity...". Moreover, when addressing shorter oligonucleotides Baulcombe et al suggest that the short fragments need to be protected from nuclease activity. Baulcombe et al do not teach each limitation of the nucleic acids of the present claimed invention. Applicants respectfully request that the Examiner withdraws the rejection under 35 U.S.C. § 102(e).

Additionally, new dependent claims 108 and 109 are not anticipated by Baulcombe et al because they are limited to human and mammalian mRNA respectively. The methods and compositions of Baulcombe et al are limited to those in plants. In fact, the discovery that the

methods of the invention work in mammalian cells was accompanied by unexpected properties. In particular, the discovery that isolated RNA of 21-23 in length was an important size limit in mammalian cells was unexpected because longer pieces of RNA induce interferon and cell death in mammalian cells (unlike plants). Additionally, these are the naturally occurring sizes that are produced by DICER in a cell and hence are most closely related to what works in nature. Thus claims 108 and 109 are not anticipated by Baulcombe et al.

Applicants note that claims 48-50 have been canceled and it is applicants understanding that claim 42 is withdrawn.

C. Claims 1-5, 12, 16, 43, and 76-95 have been rejected as being anticipated by Morrisey et al. (US 2003/0206887). According to the Examiner, US 2003/0206887 describes nucleic acids of 19 to 25 nucleotides that mediate RNAi of an mRNA to which it corresponds.

The teachings identified by the Examiner in US 2003/0206887 published patent application are not entitled to a priority date earlier than the priority date of the instant patent application. Thus the US 2003/0206887 published patent application is not prior art to the instant claims. US 2003/0206887 is a continuation-in-part of application No. PCT/US02/09187, filed on Mar. 26, 2002, and which is a continuation-in-part of application No. 09/877,478, filed on Jun. 8, 2001, now abandoned, which is a continuation-in-part of application No. 09/696,347 filed on Oct. 24, 2000, now abandoned which is a continuation-in-part of application No. 09/636,385, filed on Aug 9, 2000, now abandoned, which is a continuation-in-part of application No. 09/531,025, filed on Mar. 20, 2000, now abandoned, which is a continuation-in-part of application No. 09/436,430, filed on Nov. 8, 1999, which is a continuation of application No. 08/193,627, filed on Feb 7, 1994, now Pat. No. 6,017,756, which is a continuation of application No. 07/882,712 filed on May 14, 1992, now abandoned.

The priority applications that predate the priority date of the present claims do not disclose the nucleic acids of 19 to 25 nucleotides in length as mediators of RNAi. The first priority application of the US 2003/0206887 published patent application that predates the priority date of the instant patent application is continuation-in-part 09/531,025 filed on March 20, 2000, which does not include the length limitation in the specification. Therefore, the Morrissey reference cannot be prior art to the present application. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 102(e).

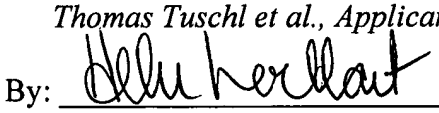
Claim Rejection Under 35 U.S.C. § 103

The Examiner has rejected claims 48-50 over Baulcombe *et al.* (US 6,531,647) for the teaching described above and Tally *et al.* (US 6,475,726) for its teaching of a method of identifying a compound that modulates the function of a component of a cell wherein the compound is isolated and purified using non-denaturing gel electrophoresis and non-denaturing column chromatography. Claims 48-50 have been canceled by this amendment. Accordingly, Applicant respectfully requests that the Examiner withdraw the claim rejection under 35 U.S.C. § 103.

Summary

It is believed that the claims are in condition for allowance. A prompt and favorable action is earnestly solicited. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,
Thomas Tuschl et al., Applicant

By: 

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